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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,385	11/12/2001	Carol W. Readhead	20040351.DIB	3519

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/008,385	**Applicant(s)** READHEAD ET AL.	
	Examiner Joanne Hama, Ph.D.	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 September 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *135,137,138,140-143 and 145-160*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Response to Arguments

With regards to the Applicant's arguments (Applicant's response, September 16, 2005, page 7) concerning the finality of the Office Action of July 26, 2005, the finality of the action is maintained because the responses to the First Action, filed August 30, 2004 and October 10, 2004 included amendment to the claims which overcame the rejections cited by the Examiner in the First Office Action, October 6, 2003, but introduced new issues of consideration. These new issues of consideration did not place the Application in condition for allowance and thus, the Applicant's amendments necessitated new grounds of rejection and brought the Application to final rejections of April 6, 2005 and July 26, 2005. It is noted that the Final Rejection of July 26, 2005 was written to address claim 160, which was inadvertently left out of the Final Rejection of April 6, 2005. Thus, making the Final Rejection was proper and the finality stands.

Applicant has submitted references and a new IDS to address the deficiencies of the IDSes submitted May 20, 2004 and August 30, 2004, cited in the Final Office Action of July 26, 2005. These references have been considered.

Applicant's arguments filed September 16, 2005 have been fully considered but they are not persuasive. The issue at hand concerns the rejection of claims 135, 137, 138, 140-143, 145-159 under 35 U.S.C. § 103(a), as being unpatentable over Brinster and Zimmermann (1994, PNAS, USA, 91: 11298-11302) in view of Vogel and Sarver (1995, Clinical Microbiology Review, 8: 406-410) and a rejection of claim 160 under 35

U.S.C. § 103(a) as being unpatentable over Brinster and Zimmer (cited above) and Vogel and Sarver (cited above) and Wivel and Walters (1993, Science, 262: 533-538).

With regards to the rejection using the teachings of Brinster and Zimmermann and Vogel and Sarver, the Applicant asserts that Brinster and Zimmerman's teachings, (namely, page 11301, second col. last parag.) are far from the positive teaching represented in the current Office Action. The Applicant points out that Brinster and Zimmermann teach that, "if spematogonia can be cultured and manipulated—eg. via targeted homologous recombination of DNA sequences—and individual modified clones of cells can be selected in a manner similar to embryonic stem cells, then these cells could be used to create mice with germ line modifications." Applicant emphasizes these underlined phrases to suggest that there is doubt in the authors' minds that this is a possibility that will work in any event. With regards to this issue, the Examiner disagrees. The Examiner used the teaching of Brinster and Zimmermann to indicate that Brinster and Zimmermann provide motivation for an artisan to use spermatogonia to introduce germline changes. Brinster and Zimmermann, in their studies, obtained spermatogonia from transgenic mice and did not generate transgenic sperm by introducing foreign DNA. As such, because this method step was never taught, the applicability of their procedure of transplanting spermatogonia comprising foreign DNA that is introduced by transfection or transduction was written hypothetically. Further, the fact that Brinster and Zimmermann discussed the issue suggests reasonable expectation of success that one could arrive at the claimed invention of transgenic spermatogonia, obtained by introducing foreign DNA via transfection or transduction.

With regards to Brinster and Zimmermann teaching that "if spermatogonia can be cultured and manipulated—e.g. via targeted homologous recombination of DNA sequences" and that Capecchi teaches an artisan how to perform homologous recombination, it should be pointed out that Brinster and Zimmermann do generally indicate that generation of transgenic sperm can be obtained in a variety of ways, including targeted homologous recombination (this is indicated by the "e.g." preceding "via targeted homologous recombination"). While Brinster and Zimmermann do not specifically include integration of virus, the art teaches that viral vectors, especially retroviral vectors, were a common way of introducing foreign DNA into a cell (Vogel and Sarver, under "Retrovirus-Mediated Gene Transfer"). The Examiner used Vogel and Sarver to point out that "unliked the previously cited studies of DNA plasmid-mediated delivery, in which the delivered genes remain unitegrated, genes transferred via retroviral vectors are inserted into the host genome, thereby ensuring the perpetuity of the genetic information in the target cells (Vogel and Sarver, page 408, 2nd col., 1st parag.; see also Final Office Action, July 26, 2005, page 7). Vogel and Sarver provide motivation to the artisan to use retroviral vectors, rather than plasmids, to introduce foreign DNA into a host cell.

The Applicant asserts that combining Brinster and Zimmermann in view of Vogel and Sarver does not add information that is more relevant to the patentability of the present claims. Further, the Vogel and Sarver reference is directed to nucleic acid vaccines which has nothing to do with making transgenic animals. The Examiner disagrees. Vogel and Sarver do not solely teach vaccines. Rather, Vogel and Sarver

teach "Retrovirus-Mediate Gene Transfer" (Vogel and Sarver, page 408) and teach that using a retrovirus is a way of introducing of a retroviral vector is a means of stably introducing a gene into the host chromosome. The Applicant also points out that nucleic acid vaccines work by the nucleic acid being able to express a polypeptide which acts as an antigen in an immune response and that there is no requirement for the nucleic acid to be in a viral vector or for it to integrate into the chromosome in order to do this. In response, certainly, while there is no requirement, Vogel and Sarver point out that one major benefit of using a retroviral vector to introduce a foreign gene is that the integration of a retroviral vector into the host genome ensures perpetuity of the genetic information in the target cells. Thus, 103 rejection of claims 135, 137, 138, 140-143, 145-159 in view of the teachings of Brinster and Zimmermann in view of Vogel and Sarver remains.

With regards to the rejection of claim 160 in view of Brinster and Zimmermann and Vogel and Sarver, in view of Wivel and Walters, the Applicant argues that claim 160 depends of claim 135 and clearly relates to "non-human vertebrate species," while Wivel and Walters discuss potential human genetic intervention. The context of Wivel and Walters is, thus, in the context of disease prevention in humans. With regards to this issue, while Wivel and Walters do not specifically point to treating diseases in non-human animals and teach that there are some human diseases which are good candidates for germ-line gene modification in humans, an artisan at the time of filing would have known that if germ-line modification had applicability in humans, it would have had applicability in non-human animals because the studies that could be

accomplished in humans are based on studies carried out in animals (see Wivel and Walters, under "Scientific Considerations"). The Applicant points out that Wivel and Walters teach the introduction of foreign DNA into the fertilized mouse egg and ES cells, they do not teach how to use male germ cells. While Wivel and Walters do not teach the stable introduction of foreign DNA into male germ cells, the combined teachings of Brinster and Zimmermann and Vogel and Sarver do. Thus, the rejection of claim 160, in view of the combined teachings of Wivel and Walters, Brinster and Zimmermann, and Vogel and Sarver remains.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER